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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/648,813	08/25/2003	Erkki Ruoslahti	066821-0233	5267

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EXAMINER	
YAO, LEI	
ART UNIT	PAPER NUMBER
1642	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	02/20/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/648,813	RUOSLAHTI ET AL.	
	Examiner	Art Unit	
	Lei Yao, Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 December 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *99-107,110-125 and 178-199* is/are pending in the application.

4a) Of the above claim(s) *114-117,124-177* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *99-107,110-113,118-123 and 178-199* is/are rejected.

7)☒ Claim(s) *187 and 199* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☒ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *exhibit A*.

REQUEST FOR CONTINUED EXAMINATION

The request filed on 11/17/06 for a Continued Examination (RCE) under 37 CFR 1.114 based on Application No. 10648813 is acceptable, and a RCE has been established. An action on the RCE follows.

The Amendment filed on 12/19/06 is acknowledged and has been entered. Claims 1-98,108, 109, and 126-177 have been cancelled. Claims 178-199 are added. Claims 99-107, 110-125, 178-199 are pending. Claims 114-117, 124, and 125 have been withdrawn previously. Claims 99-107, 110-113, 118-123 and 178-199 are under consideration.

Sequence Requirements

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R. § 1.821(a)(1) and (a)(2). This application fails to comply with the requirements of 37 C.F.R. §§ 1.821-1.825. The disclosure contains sequences that need SEQ ID numbers on page 23, lines 25 and 27, page 57, line 22. If these sequences are found in the sequence listing filed 8/26/03, applicants need only insert the appropriate SEQ ID Nos. However, if these sequences are not part of the listing, then applicants need to comply with the sequence rules. Applicant is reminded to check the entire disclosure to ensure that the application is in sequence compliance. Any questions regarding compliance with the sequence rules requirements specifically should be directed to the departments listed at the bottom of the Notice to Comply (see attached form, PTO L90).

Claim Rejections - 35 USC § 112

The following is a quotation of the **second paragraph** of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 102-113, 118-123, and 188-199 recites the limitation "said peptide " in claim 102. There is insufficient antecedent basis for this limitation in the claim. Claim 102 recites a conjugate comprising a therapeutic agent linked to a homing molecule comprising the amino acid CREKA (SEQ ID NO: 1). It is not clear whether or not "said peptide" is the homing molecule comprising the amino acid sequence

CREKA (SEQ ID NO: 1). Correction or clarification is required. Claim 102 renders its dependent claims indefinite.

The following is a quotation of the **first paragraph** of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Written Description:

Claims 99-107, 110-113, 118-123 remain and claims 178-186, 188-198 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are broadly drawn to a peptide comprising a peptide, CREKA (SEQ ID NO: 1), having less than 7, 8, 9, 10, 15, 20, 25, 30, 35, 40, 50, or 100 amino acid residues, wherein peptides selectively homes to tumor vasculature and selectively binds collage, or a conjugate comprising a therapeutic agent linked to one or at least two of the peptides above. Thus, the claims are inclusive of a genus of peptides having amino acid residues between 6-100 at length comprising five amino acids, CREKA (SEQ ID NO: 1) and a genus of conjugates linked to the peptides above. However, the specification on page 73-75 only reasonably conveys one species of homing molecule, a peptide, CREKA (SEQ ID NO:1) associated with collagen binding in the tumor. However, the term "comprising" in the claims are open-ended. It expands the sequence of SEQ ID NO: 1 to include additional non-disclosed amino acid residues (from 1-95) outside of the sequence shown in SEQ ID NO: 1. Therefore, the instant claims encompass in their breadth any protein comprising amino acid sequence disclosed in SEQ ID NO: 1 and additional unknown amino acid residues. The specification neither provide any peptide towards a genus of the peptide having amino acid residues 6-100 comprising CREKA, SEQ ID NO: 1, nor sufficient enabling description of those peptide associated with collagen binding and homing activities. Description of a genus may be achieved by means of a recitation of a representative number of species falling within the scope of the genus or by

describing structural features common the genus that "constitute a substantial portion of the genus." See University of California v. Eli Lilly and Co., 119 F.3d 1559, 1568, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997): "A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNA, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus."

The court has since clarified that this standard applies to compounds other than cDNAs. See University of Rochester v. G.D. Searle & Co., Inc., __F.3d__,2004 WL 260813, at *9 (Fed.Cir.Feb. 13, 2004). The instant specification fails to provide sufficient descriptive information, such as definitive structural or functional features and representative number of the species that are common to the genus of homing peptides comprising sequence CREKA (SEQ ID NO: 1) and containing 6-100 amino acid residues, which homes to tumor vasculature and selectively binds to collagen. Since the disclosure fails to describe the common attributes or characteristics that identify members of the genus, and because the genus is highly variant, the disclosure of peptide CREKA (SEQ ID NO: 1) is insufficient to describe the genus having more amino acids attached to either or both sides of the peptide maintaining such claimed function. Thus, one of skill in the art would reasonably conclude that the inventor(s), at the time the application was filed, **did not have** possession of the claimed invention.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116). As discussed above, the skilled artisan could not envision the detailed chemical structure(s) of the encompassed genus of *a* homing peptides or conjugates having less than 7, 8, 9, 10, 15, 20, 25, 30, 35, 40, 50, or 100 amino acid residues comprising CREKA peptide (SEQ ID NO: 1), which could maintain the same function as CREKA. Therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a

mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence. Therefore, only the peptide, *CREKA (*SEQ ID NO: 1) and conjugate comprising therapeutic agent linked to the peptide of SEQ ID NO:1, but not the full breadth of the claims, meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112 paragraph 1" Written Description" Requirement. Applicant is invited to point to clear support or specific examples of the claimed invention in the specification as filed.

In the response to the final rejection filed on 9/18/06, applicants argue *that the peptide expressed on the surface of the phage as a fusion with a phage protein, a product of peptide-gene III, exemplary of a peptide comprising CREKA (SEQ ID NO: 1).* This has been carefully considered but is deemed not to be persuasive. It is well known and widely used that a phage gene III protein is fused to a homing peptide, carries the foreign peptide incorporated into virions during the phage display, and served as infective and productive function. One skilled in the art has proved the gene III product self has no function for or an effect on homing to any tissues or binding to a receptor expressed in the mammalian cells. However, claimed peptides having less than 7, 8, 9, 10, 15, 20, 25, 30, 35, 40, 50, or 100 amino acid residues comprising CREKA of SEQ ID NO:1 could be any peptides having 6-100 amino acids attached to either or both sides of the CREKA and homing to tumor vasculartur and binding to collagen IV. Instant specification as filed does not provide any of such peptides having the same function as CREKA. In addition, Simth et al., (Chem Rev, vol 97, page 391-410) teach phage display system for screening a peptide comprising homing molecule and indicate when the gene display a relative large foreign peptide (more than eight amino acids), it will not support phage production and produce mosaic particles (page

393, col 2). Thus, one skilled in the art has recognized that the peptides comprising homing peptide in phase display is limited to the certain size and/or the certain sequence in order to perform the certain function. Instant specification does not provide any other peptide having 6-100 amino acids comprising CREKA (SEQ ID NO:1) could be fused to Gene III and home to tumor vasculature and bind to collagen.

Applicants further argue that *the second structure of large peptide comprising CREKA is not relevant to the claimed peptide because the claims have been amended to the peptide selectively homing to tumor vasculature and newly added claims (178-199) recite smaller peptides.* In response to this argument, although the functional language is added to amended claims, applicants have not provided any of the claimed peptides (6-100 amino acids) having such function or could perform such function due to the concern of the limitation of phase display discussed above. Since the disclosure does not provide the sequence of the claimed peptide and the peptide is highly variants, the disclosure of peptide CREKA (SEQ ID NO:1) is insufficient to describe the genus of the peptides comprising CREKA. Thus, one of skill in the art would reasonably conclude that the inventor(s), at the time the application was filed, **did not have** possession of the claimed peptides. Thus, Applicant's argument has not been found persuasive, and the rejection is maintained and stated again above.

As drawn to scope of enablement

Claims 99-107, 110-113, 118-123, 178-186, 188-198 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the peptide, CREKA of SEQ ID NO:1, homing to tumor vasculature and selectively binding collagen and a conjugate comprising the peptide, CREKA (SEQ ID NO:1), linked to a cytotoxic agent or antiangiogenic agent, does not reasonably provide enablement for the other peptides having less than 7, 8, 9, 10, 15, 20, 25, 30, 35, 40, 50, or 100 amino acid residues comprising CREKA of SEQ ID NO:1 and a conjugate comprising the peptides above. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The factor considered when determining if the disclosure satisfies the enablement requirement and whether any is undue include, but are not limited to: 1) nature of the invention, 2) state of the prior

art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of necessary experimentation claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. *In re wands,* 858 F.2d 731, 737.8 USPQ2d 1400, 1404 (Fed. Cir.1988).

The claims are broadly drawn to a homing peptide having less than 7, 8, 9, 10, 15, 20, 25, 30, 35, 40, 50, or 100 amino acid residues comprising five amino acids CREKA (SEQ ID NO:1) or a conjugate comprising the peptide having an amino acid sequence less than 100 residues comprising linked to a therapeutic agent comprising a cytotoxic agent or anti-angiogenic molecule. To satisfy the requirement of 112, 1st paragraph, it is necessary that the specification provides an enabling disclosure of how to make and use a claimed invention. The specification on page 73-75 teaches only one species of homing molecule, a peptide, CREKA (SEQ ID NO:1) associated with collagen binding in the tumor. However, the term "comprising" in the claims are open-ended. It expands the sequence of SEQ ID NO: 1 to include additional non-disclosed amino acid residues (from 1-95) outside of the sequence shown in SEQ ID NO: 1. Therefore, the instant claims encompass in their breadth any protein comprising amino acid sequence disclosed in SEQ ID NO: 1 and additional unknown amino acid residues. The specification does not teach any peptide sequence having less than 7, 8, 9, 10, 15, 20, 25, 30, 35, 40, 50, or 100 amino acid residues comprising CREKA (SEQ ID NO: 1), wherein the additional amino acid is located at any position of the peptide, the specification does not teach any peptide at any length (6-100 amino acids) comprising CREKA would retain the activity of binding to collagen and homing to tumor vasculature. The specification does not provide any working example, which enable any peptide or any conjugate linked to a peptide having less than 100 amino acid residues comprising CREKA (SEQ ID NO: 1) in the claims, which is incorporated into the virion, binds to collagen, or homes to tumor vasculature in the phage display. Thus, one skilled in the art would not know how to use or even make a peptide based on the claims for tumor vasculature homing and binding to collagen IV without undue experimentation.

It is well known in the art that proteins are folded 3-dimensional structures, the function and stability of which are directly related to a specific conformation (Mathews and Van Holde, Biochemistry, 1996, pp. 165-171). In any given protein, amino acids distant from one another in the primary sequence

may be closely located in the folded, 3-dimensional structure (Mathews and Van Holde, Biochemistry, 1996, pp. 166, figure 6.1). It is also know in the art that even a single modification or substitution in a protein sequence can alter the protein function. Protein chemistry is probably one of the most unpredictable areas of biotechnology. For example, the replacement of a single lysine at position 118 of the acidic fibroblast growth factor by a glutamic acid led to a substantial loss of heparin binding, receptor binding, and biological activity of the protein (Burgess et al, Journal of Cell biology, Vol 111, p2129-2138, 1990). In transforming growth factor alpha, replacement of aspartic acid at position 47 with asparagines, does not affect biological activity while the replacement with serine or glutamic acid sharply reduce the biological activity of the mitogen (Lazar et al., Molecular and Cellular Biology, vol 8, p1247-1252, 1988). These references demonstrate that even a single amino acid substitution or what appears to be an inconsequential chemical modification, will often dramatically affect the biological activity of the protein.

Furthermore, Shimkets et al., (WO200192523, Publication date, 12/6/2001, see search result attached, exhibit A)) teach a peptide having 52 amino acid residues comprising CREKA of SEQ ID NO: 1, which is involved in diagnosing preventing or treating cardiovascular, neurodegenerative, or proliferative diseases. Shimkets et al., do not record the peptide having function of homing to tumor vasculature and binding to collagen. Thus, one skilled in the art has not recognized a peptide having less than 100 amino acids at length comprising amino acids CREKA would bind to a collagen and homing to tumor because treating disease like neurodenerative disease do not require binding or homing to tumor vascular.

No direction, guidance, or working example is provided in current specification to assist one skilled in the art using the claimed peptides and conjugate having less than 7, 8, 9, 10, 15, 20, 25, 30, 35, 40, 50, or 100 amino acid residues comprising 5 basic amino acids CREKA (SEQ ID NO: 1 for binding to a collagen and homing to tumor vasculature. In view of the lack of the predictability of the art to which the invention pertains as evidenced by the arts taught above, one skilled in the art would be forced into under experimentation in order to practice the claimed invention.

Claim Objections

Claims 187 and 199 are objected to as being dependent from rejected base claims. These claims appear to be allowable if 35 USC 112 2nd rejection is obviated and the claims are rewritten in closed language as base claims, i.e. An isolated peptide consisting of the amino acid sequence of SEQ ID NO: 1 (for claim 187) and a conjugate comprising a cytotoxic or anti-angiogenic agent linked to the homing molecule consisting of the amino acid sequence of SEQ ID NO: 1 (for claim 199).

Conclusion

No claims are allowed.

The peptide of CREKA (SEQ ID NO: 1) is free of art. The closest prior art for the base claim, claim 99, is Shimkets et al., (WO200192523, Publication date, 12/6/2001) teach a peptide having 52 amino acid residues comprising CREKA of SEQ ID NO: 1, Shimkets et al., do not teach or suggest the peptide having function of homing to tumor vasculature and binding to collagen.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lei Yao, Ph.D. whose telephone number is 571-272-3112. The examiner can normally be reached on 8am-6.00pm Monday-Thursday.

Any inquiry of a general nature, matching or file papers or relating to the status of this application or proceeding should be directed to Kim Downing for Art Unit 1642 whose telephone number is 571-272-0521

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shanon Foley can be reached on 571-272-0898. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Lei Yao,
Examiner
Art Unit 1642

LY

SHANON FOLEY
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

Notice to Comply	Application No. 10648813	Applicant(s) Ruoslahti et al	
	Examiner Lei Yao	Art Unit 1642	

NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

Applicant must file the items indicated below within the time period set the Office action to which the Notice is attached to avoid abandonment under 35 U.S.C. § 133 (extensions of time may be obtained under the provisions of 37 CFR 1.136(a)).

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825 for the following reason(s):

☐ 1. This application clearly fails to comply with the requirements of 37 C.F.R. 1.821-1.825. Applicant's attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990). If the effective filing date is on or after July 1, 1998, see the final rulemaking notice published at 63 FR 29620 (June 1, 1998) and 1211 OG 82 (June 23, 1998).

☐ 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 C.F.R. 1.821(c).

☐ 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 C.F.R. 1.821(e).

☐ 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 C.F.R. 1.822 and/or 1.823, as indicated on the attached copy of the marked -up "Raw Sequence Listing."

☐ 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A Substitute computer readable form must be submitted as required by 37 C.F.R. 1.825(d).

☐ 6. The paper copy of the "Sequence Listing" is not the same as the computer readable from of the "Sequence Listing" as required by 37 C.F.R. 1.821(e).

☒ 7. Other: need SEQ ID numbers for sequences on page 23 and 57..

Applicant Must Provide:

☐ An initial or substitute computer readable form (CRF) copy of the "Sequence Listing".

☒ An initial or substitute paper copy of the "Sequence Listing", **as well as an amendment specifically directing its entry into the application.**

☒ A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

For questions regarding compliance to these requirements, please contact:.

For Rules Interpretation, call (703) 308-4216 or (703) 308-2923
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